Attachment 2: Re-evaluation of Dietary Endpoint and Non-dietary Endpoint Selection and Dermal Absorption Factor; Report of the Hazard Identification Assessment Review Committee

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MEMORANDUM

SUBJECT: ***METHYL PARATHION*** - Re-evaluation of Dietary Endpoint and Non-dietary Endpoint Selection and Dermal Absorption Factor; Report of the Hazard Identification Assessment Review Committee

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On March 4, 1999 the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) reevaluated the endpoints selected for dietary and non-dietary risk assessment and the dermal absorption factor for methyl parathion. The HIARC's conclusions are presented in this report.

ACUTE REFERENCE DOSE (RfD)

Previously, the Committee had selected the acute oral neurotoxicity study for use in acute dietary risk assessment (HIARC Report, 12/1/97). Effects seen at 7.5 mg/kg (the mid-dose) in this study included cholinesterase inhibition, changes in functional observation battery and motor activity, and neuropathology. Therefore, the NOAEL from this study was set at 0.025 mg/kg (the low dose). Because the mid and low doses used in this study differed by a factor of 300, the registrant requested reconsideration of this endpoint, and suggested several possible alternatives.

On March 4, 1999, the Committee evaluated available data for methyl parathion, and concluded the only appropriate study demonstrating a higher NOAEL for the endpoints measured in the acute neurotoxicity study was the special one year chronic neurotoxicity study. The study included a dose intermediate between the LOAEL and NOAEL of the guideline subchronic neurotoxicity study (0.295 and 0.029 mg/kg/day, respectively, based on red blood cell cholinesterase inhibition), and critical endpoints identified in the acute oral neurotoxicity study (cholinesterase inhibition and neuropathology) were evaluated.

In the one year special neurotoxicity study, methyl parathion was administered in the diet at 0, 0.5, 2.5, 12.5, and 50 ppm (0, 0.02, 0.107, 0.533, and 2.207 mg/kg/day for males, 0, 0.026, 0.138, 0.697, and 3.088 mg/kg/day for females) for one year. The NOAEL for the study was 2.5 ppm (0.107 mg/kg/day for males, 0.138 mg/kg/day for females), and the LOAEL 12.5 ppm (0.533 or 0.697 mg/kg/day for males or females, respectively), based on inhibition of plasma, brain, and red blood cell cholinesterase (in one or both sexes) and neuropathology seen in both sexes. The Committee felt that use of this study for acute dietary risk assessment would not underestimate the risk for that type of exposure, due to the longer duration of the selected study (one year vs. a single exposure) and the evaluation of the critical effects (cholinesterase inhibition and neuropathology). The Committee felt that use of a NOEL from a long term (one year) study would be protective for a single exposure.

Calculation of Acute RfD:

NOAEL = 0.11 mg/kg

Uncertainty Factors: 10 (interspecies) X 10 (intraspecies)
= 100

Acute RfD = 0.0011 mg/kg/day

CHRONIC REFERENCE DOSE (RfD)

The Committee also considered the registrant's proposal that the one year special chronic neurotoxicity study be used for the chronic dietary risk assessment. The current chronic RfD, 0.0002 mg/kg/day, is based the NOAEL of 0.02 mg/kg/day in a 2-year chronic rat study; red blood cell cholinesterase inhibition, neuropathology, and hematologic effects were seen at the LOAEL of 0.2 mg/kg/day (see HIARC report, 12/1/97). The NOAEL from the one year neurotoxicity study (0.11 mg/kg/day) is higher than the NOAEL in the chronic study, but lower than the LOAEL for that study. However, hematologic effects (seen at the LOAEL in the 2 year chronic study) were not evaluated in the one year study, therefore the Committee could not be sure that these effects did not occur at levels lower than the NOAEL for the one year study. Thus, the Committee determined that there should be no change in the chronic RfD, which will remain at 0.02 mg/kg/day.

Calculation of Chronic RfD:

NOAEL = 0.02 mg/kg/day

Uncertainty Factors: 10 (interspecies) X 10 (intraspecies)
= 100

Chronic RfD = 0.0002 mg/kg/day

DERMAL TOXICITY ENDPOINTS

For reasons described in the previous HIARC report (12/1/97), it was determined that the 21-day rabbit dermal toxicity studies were not appropriate for use as dermal toxicity endpoints. Previously, the acute oral neurotoxicity study was selected for use as the short term dermal endpoint, the two-year chronic rat study was selected for both intermediate and long term dermal endpoints.

Based on the rationale outlined above, the Committee selected the one-year chronic neurotoxicity study for use in short and intermediate-term dermal risk assessment. There is no change in the endpoint selected for long term dermal risk assessment. Since oral values were selected, a dermal absorption factor of 100% should be used for risk assessments.

Short- and Intermediate-Term Dermal Risk Assessment:

NOAEL = 0.11 mg/kg
MOE = 100

Long Term Dermal Risk Assessment:

As determined previously, the Committee reaffirmed that the 2-year chronic rat study will be used for long term dermal risk assessment.

NOAEL = 0.02 mg/kg/day
MOE = 100

Dermal Absorption Factor:

The Committee reaffirmed that the dermal absorption factor for methyl parathion would be 100% (assume equivalent dermal and oral absorption). The decision was based on the following data, some of which has been submitted since the previous HIARC meeting (see Table 1).

Table 1. Comparison of cholinesterase inhibition at selected doses in females from oral and dermal studies in rats and rabbits.

Study type	MRID No.	Dose (mg/kg/day)	Percent Inhibition in various compartments		
			Red Blood Cell	Plasma	Brain
Rabbit					
Oral Developmental	?	3	19	12	---
Oral Developmental	44691004	3	43	---	ND
Oral Developmental	44691004	9	75	50	ND
21-Day Dermal	42263701	10	30	---	---
21-Day Dermal	42263701	100	38	15	---
Rat					
Oral Developmental	41136101	3	71	59	22
Acute Oral Neurotoxicity (peak effect time)	43254401	7.5	57	71	80
Acute Oral Neurotoxicity (peak effect time)	43254401	15	58	76	90
Subchronic Oral Neurotoxicity (4 week time point)	43490501	3.96	64	80	80
Two-week Dermal Neurotoxicity (preliminary data submission)	44680200	3.5 (a.i.)	72	38	60
Two-week Dermal Neurotoxicity (preliminary data submission)	44680200	7.5 (a.i.)	85	50	80

ND=not done; ---=no inhibition found

Although the rabbit appeared to demonstrate less cholinesterase inhibition after dermal doses than oral doses (compare oral developmental at 9 mg/kg/day with dermal at 10 mg/kg/day), the rat showed comparable inhibition after similar oral and dermal doses (compare oral developmental at 3 mg/kg/day with two week dermal neurotoxicity study at 3.5 mg/kg/day). The Committee believes that these data support the use of an assumption of 100% dermal absorption (e.g. equivalent dermal and oral absorption).

In addition, the Committee noted the similarity in the doses selected for the new short term rat dermal and oral studies currently being conducted by the registrant (oral study will use 0, 1, 1.5, 3, and 12 mg/kg; dermal study will use 0, 1, 2, and 3 mg/kg/day). Use of similar doses in the oral and dermal studies supports the assumption of similar toxicity by the oral and dermal routes.

The Committee also noted the preliminary nature of the data from the two week dermal neurotoxicity study and the pending completion of the two new studies. The above conclusions will be reevaluated if indicated when complete data from these studies are received.

INHALATION ENDPOINTS

The Committee determined that inhalation risk assessments should be conducted using the same oral values used in acute and chronic dietary risk assessment, for the appropriate time frames. As specified in the previous report, the inhalation exposure should be converted to oral dose, which is then compared with the appropriate endpoints as described above.

FQPA FACTOR

As determined previously, the 10x FQPA safety factor was retained for methyl parathion (see HIARC report, 7/7/98, FQPA Safety Factor Committee report 8/6/98).

SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below:

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL= 0.11 mg/kg UF = 100	Based on Plasma, RBC, and Brain ChEI and neuropathology	Chronic Neurotoxicity in rat
	Acute RfD = 0.0011 mg/kg		
Chronic Dietary	NOAEL = 0.02 mg/kg/day UF = 100	Based on Plasma, RBC, and Brain ChEI; neuropathology; and hematological effects	Two-year chronic toxicity/oncogenicity in rat
		Chronic RfD = 0.0002 mg/kg day	
Short-Term[1] (Dermal)	Oral NOAEL= 0.11 mg/kg	Based on Plasma, RBC, and Brain ChEI and neuropathology	Chronic Neurotoxicity in rat
Intermediate-Term[1] (Dermal)	Oral NOAEL= 0.11 mg/kg	Based on Plasma, RBC, and Brain ChEI and neuropathology	Chronic Neurotoxicity in rat
Long-Term (Dermal)[1]	Oral NOAEL= 0.02 mg/kg/day	Based on Plasma, RBC, and Brain ChEI; neuropathology; and hematological effects	Two-year chronic toxicity/oncogenicity in rat
Short Term[2] (Inhalation)	Oral NOAEL= 0.11 mg/kg	Based on Plasma, RBC, and Brain ChEI and neuropathology	Chronic Neurotoxicity in rat
Intermediate Term[2] (Inhalation)	Oral NOAEL= 0.11 mg/kg	Based on Plasma, RBC, and Brain ChEI and neuropathology	Chronic Neurotoxicity in rat
Long Term[2] (Inhalation)	Oral NOAEL= 0.02 mg/kg/day	Based on Plasma, RBC, and Brain ChEI; neuropathology; and hematological effects	Two-year chronic toxicity/oncogenicity in rat

1. Use 100% Dermal Absorption for Route-to-Route Extrapolation

2. Use 100% Absorption for Route-to-Route Extrapolation